=> d l5 ti 1-54

L5 ANSWER 1 OF 54 WPIDS (C) 2003 THOMSON DERWENT
TI Novel protein Ozz and nucleic acid encoding the protein involved in development and function of muscle, useful as target for identifying drugs effective in treating myogenesis disorders.

L5 ANSWER 2 OF 54 WPIDS (C) 2003 THOMSON DERWENT
TI Novel nucleic acid molecule encoding secreted or membrane-associated proteins useful for identifying modulators and for treating disorders associated with spleen, bone, kidney, liver, pituitary and thyroid gland.

L5 ANSWER 3 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Processing of lysosomal beta-galactosidase: The C-terminal precursor fragment is an essential domain of the mature enzyme.

L5 ANSWER 4 OF 54 CAPLUS COPYRIGHT 2003 ACS
TI Inherited metabolic diseases caused by the genetic defect of protective protein/cathepsin A and lysosomal sialidase

L5 ANSWER 5 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Structural and functional study of K453E mutant **protective protein/cathepsin A** causing the late infantile form of **galactosialidosis**.

L5 ANSWER 6 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Endothelin-1 in the brain of patients with galactosialidosis: Its abnormal increase and distribution pattern.

L5 ANSWER 7 OF 54 CAPLUS COPYRIGHT 2003 ACS
TI Protein **PPCA** (protective protein/catepsin A) and endothelin 1 in **galactosialidosis**

L5 ANSWER 8 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Stable expression of **protective protein/cathepsin A**-Green fluorescent protein fusion genes in a fibroblastic cell line from a **galactosialidosis** patient: Model system for revealing the intracellular transport of normal and mutated lysosomal enzymes.

L5 ANSWER 9 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Molecular basis of GM1 gangliosidosis and Morquio disease, type B. Structure-function studies of lysosomal beta-galactosidase and the non-lysosomal beta-galactosidase-like protein.

L5 ANSWER 10 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Early-infantile galactosialidosis: Prenatal presentation and postnatal follow-up.

L5 ANSWER 11 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Correction of murine **galactosialidosis** by bone marrow-derived macrophages overexpressing human **protective protein/cathepsin A** under control of the colony-stimulating factor-1 receptor promoter.

L5 ANSWER 12 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Lack of **PPCA** expression only partially coincides with lysosomal storage in **galactosialidosis** mice: Indirect evidence for spatial requirement of the catalytic rather than the protective function of **PPCA**.

L5 ANSWER 13 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Transport of human lysosomal neuraminidase to mature lysosomes requires protective protein/cathepsin A.

L5 ANSWER 14 OF 54 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Bicistronic retroviral vector coexpressing lysosomal **protective protein cathepsin A** and GFP for gene therapy of **galactosialidosis**

L5 ANSWER 15 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI The atomic model of the human **protective protein/cathepsin A** suggests a structural basis for **galactosialidosis**.

L5 ANSWER 16 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI A point mutation in the neu-1 locus causes the neuraminidase defect in the SM/J mouse.

L5 ANSWER 17 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Bicistronic retroviral vector coexpressing lysosomal **protective protein/cathepsin A** and GFP for gene therapy of **galactosialidosis**.

L5 ANSWER 18 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
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L5 ANSWER 19 OF 54 WPIDS (C) 2003 THOMSON DERWENT
TI Crystallising a human protective protein/cathepsin A or precursor - to determine three dimensional structure by x-ray crystallography and computer analysis to identify ligands for PPCA-related pathologies.

L5 ANSWER 20 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Identification of the promoters for the human and murine protective protein/cathepsin A genes.

L5 ANSWER 21 OF 54 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Corrigendum: Molecular and biochemical analysis of **protective protein/cathepsin A** mutations: Correlation with clinical severity in **galactosialidosis** (Human Molecular Genetics (1996) 5 (1977-1987))

L5 ANSWER 22 OF 54 CAPLUS COPYRIGHT 2003 ACS
TI Molecular and biochemical analysis of **protective protein /cathepsin A** mutations: correlation with clinical severity in **galactosialidosis**. [Erratum to document cited in CA126:153428]

L5 ANSWER 23 OF 54 SCISEARCH COPYRIGHT 2003 ISI (R)
TI Molecular and biochemical analysis of **protective protein /cathepsin A** mutations: Correlation with clinical severity in **galactosialidosis** (vol 5, pg 1977, 1996)

L5 ANSWER 24 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Fetal diagnosis of **galactosialidosis** (**protective protein/cathepsin A** deficiency.

L5 ANSWER 25 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Characterization of human lysosomal neuraminidase defines the molecular basis of the metabolic storage disorder sialidosis.

L5 ANSWER 26 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Molecular and biochemical analysis of **protective protein /cathepsin A** mutations: Correlation with clinical severity in **galactosialidosis**.

L5 ANSWER 27 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Cathepsin A deficiency in galactosialidosis: Studies of patients with carriers in 16 families.

L5 ANSWER 28 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Early-infantile galactosialidosis: Clinical, biochemical, and molecular observations in a new patient.

L5 ANSWER 29 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Correction of murine **galactosialidosis** phenotype following transplantation with bone marrow from transgenic mice over-expressing human **PPCA**.

L5 ANSWER 30 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Mouse model for the lysosomal disorder galactosialidosis and correction of the phenotype with overexpressing erythroid precursor cells.

L5 ANSWER 31 OF 54 SCISEARCH COPYRIGHT 2003 ISI (R)
TI X-RAY STRUCTURE OF THE HUMAN **PROTECTIVE PROTEIN CATHEPSIN-A** PRECURSOR - THE DEFECTIVE PROTEIN IN THE LYSOSOMAL STORAGE DISEASE **GALACTOSIALIDOSIS**

L5 ANSWER 32 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI X-ray structure of the human **protective protein cathepsin A** precursor: The defective protein in the lysosomal storage disease **galactosialidosis**.

L5 ANSWER 33 OF 54 DGENE (C) 2003 THOMSON DERWENT
TI Novel nucleic acid molecule encoding secreted or membrane-associated proteins useful for identifying modulators and for treating disorders associated with spleen, bone, kidney, liver, pituitary and thyroid gland

L5 ANSWER 34 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 43 OF 54 DGENE (C) 2003 THOMSON DERWENT

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L5 ANSWER 44 OF 54 DGENE (C) 2003 THOMSON DERWENT
TI Crystallising a human protective protein/cathepsin A or precursor - to determine three dimensional structure by x=ray crystallography and computer analysis to identify ligands for PPCA-related pathologies

L5 ANSWER 45 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 46 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 47 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 48 OF 54 DGENE (C) 2003 THOMSON DERWENT
TI Novel nucleic acid molecule encoding secreted or membrane-associated proteins useful for identifying modulators and for treating disorders associated with spleen, bone, kidney, liver, pituitary and thyroid gland

L5 ANSWER 49 OF 54 DGENE (C) 2003 THOMSON DERWENT
TI Novel nucleic acid molecule encoding secreted or membrane-associated proteins useful for identifying modulators and for treating disorders associated with spleen, bone, kidney, liver, pituitary and thyroid gland

L5 ANSWER 50 OF 54 DGENE (C) 2003 THOMSON DERWENT
TI Novel nucleic acid molecule encoding secreted or membrane-associated proteins useful for identifying modulators and for treating disorders associated with spleen, bone, kidney, liver, pituitary and thyroid gland

L5 ANSWER 51 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 52 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 53 OF 54 DGENE (C) 2003 THOMSON DERWENT
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L5 ANSWER 54 OF 54 DGENE (C) 2003 THOMSON DERWENT
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     (FILE 'HOME' ENTERED AT 12:26:00 ON 13 MAR 2003)

     FILE 'CAOLD, CAPLUS, CASREACT, CROPU, DGENE, DPCI, ENCOMPPAT, ENCOMPPAT2,
     EUROPATFULL, IFIPAT, INPADOC, JAPIO, PAPERCHEM2, PATDD, PATDPA, PATOSDE,
     PATOSEP, PATOSWO, PCTFULL, PIRA, RAPRA, SYNTHLINE, TULSA, TULSA2,
     USPATFULL, USPAT2, WPIDS' ENTERED AT 12:26:29 ON 13 MAR 2003
L1          267 S GALACTOSIALIDOSIS OR (SIALIC ACIDS (L) GALACTOSIALIDOSIS)
L2           55 S L1 (L) (PROTECTIVE PROTEIN CATHEPSIN A OR PPCA)
L3           48 DUP REM L2 (7 DUPLICATES REMOVED)
L4           43 S L3 AND PY<2001
L5            3 S L4 AND PHARMA?
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=> d ibib ab 1-3

L5 ANSWER 1 OF 3 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2000066733 PCTFULL ED 20020515
TITLE (ENGLISH): PROTEIN SPECIFIC FOR CARDIAC AND SKELETAL MUSCLE
TITLE (FRENCH): PROTEINE SPECIFIQUE DES MUSCLES CARDIAQUE ET SQUELETTIQUE
INVENTOR(S): D'AZZO, Alessandra;
BONGIOVANNI, Antonella;
NASTASI, Tommaso
PATENT ASSIGNEE(S): ST. JUDE CHILDREN'S RESEARCH HOSPITAL;
D'AZZO, Alessandra;
BONGIOVANNI, Antonella;
NASTASI, Tommaso
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000066733	**A1**	**20001109**

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US11900 A 20000428
PRIORITY INFO.: US 1999-60/131,814 19990429

ABEN The present invention relates to a muscle-specific protein, Ozz, and nucleic acids encoding the protein, that regulates development and function of muscle cells. The invention further relates to muscle-specific regulated expression of the protein, and of heterologous genes under control of the same regulatory sequences. In a specific example, a murine Ozz protein of 285 amino acids is preferentially expressed by a 1.0 kb mRNA in heart and skeletal muscle. This protein shares significant homology with neuralized proteins, and associates with a number of muscle proteins, including β-catenin.

ABFR La presente invention concerne une proteine specifique du muscle, appelee Ozz, et des acides nucleiques codant pour cette proteine qui regule le developpement et les fonctions des cellules musculaires. En outre, cette invention concerne l'expression regulee specifique du muscle de la proteine, et des genes heterologues sous controle des memes sequences regulatrices. Dans un exemple specifique, une proteine Ozz murine de 285 acides amines est, de preference, exprimee par un ARNm de 1,0 kb dans les muscles cardiaque et squelettique. Par ailleurs, cette proteine partage avec les proteines neutralisees une importante homologie, et s'associe a un certain nombre de proteines musculaires, y compris la β-catenine.

L5 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2000039150 PCTFULL ED 20020515
TITLE (ENGLISH): SECRETED PROTEINS AND USES THEREOF
TITLE (FRENCH): PROTEINES SECRETEES ET LEURS UTILISATIONS
INVENTOR(S): SHARP, John, D.
PATENT ASSIGNEE(S): MILLENNIUM PHARMACEUTICALS, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000039150	**A2**	**20000706**

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US31158 A 19991229
PRIORITY INFO.: US 1998-09/223,094 19981230

ABEN The invention provides isolated nucleic acid molecules, designated TANGO 221, TANGO 222, TANGO 176, and TANGO 232, which encode wholly secreted or membrane-associated proteins. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

ABFR Cette invention a trait a des molecules d'acide nucleique isolees, designees sous le nom de TANGO 221, TANGO 176, et TANGO 232 codant des proteines entierement secretees ou associees a des membranes. Elle porte, de surcroit, sur des molecules d'acide nucleique antisens, sur des vecteurs d'expression contenant les molecules d'acide nucleique de l'invention, des cellules hotes dans lesquelles les vecteurs d'expression ont ete introduits et des animaux transgeniques chez qui une molecule d'acide nucleique de l'invention a ete introduite ou disloquee. Elle concerne, en outre, des polypeptides isoles, des polypeptides de fusion, des peptides antigeniques et des anticorps. Il est encore question, dans cette invention, de methodes diagnostiques, de criblage et de methodes therapeutiques utilisant des compositions de l'invention.

L5 ANSWER 3 OF 3 PCTFULL
ACCESSION NUMBER: 1997015588 PCTFULL ED 20020514
TITLE (ENGLISH): **PROTECTIVE PROTEIN**/**CATHEPSIN A** AND PRECURSOR: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION AND RATIONAL DRUG DESIGN
TITLE (FRENCH): PROTEINE/CATHEPSINE A PROTECTRICE ET PRECURSEUR: CRISTALLISATION, DIFFRACTION DES RAYONS X, DETERMINATION DE STRUCTURE TRIDIMENSIONNELLE ET ELABORATION RATIONNELLE DE SUBSTANCES THERAPEUTIQUES
INVENTOR(S): RUDENKO, Gabrielle; D'AZZO, Alessandra; HOL, Wim, G., J.
PATENT ASSIGNEE(S): RUDENKO, Gabrielle; D'AZZO, Alessandra; HOL, Wim, G., J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9715588	**A1**	**19970501**

DESIGNATED STATES
W: AU CA JP US AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1996-US17325 A 19961025

PRIORITY INFO.: US 1995-60/005,976 19951026
US 1995-60/006,802 19951115

ABEN The present invention provides crystallized **protective protein/cathepsin A** (**PPCA**), a precursor thereof (pPPCA) or at least one subdomain thereof; methods for x-ray diffraction analysis to provide x-ray diffraction patterns of sufficiently high resolution for three-dimensional structure determination of the protein, as well as methods for rational drug design (RDD), based on using amino acid sequence data and/or x-ray crystallography data provided on computer readable media, as analyzed on a computer system having suitable computer algorithms.

ABFR On decrit la proteine/cathepsine A (**PPCA**) protectrice et cristalllisee, un de ses precurseurs (pPPCA) et au moins un de ses sous-domaines, des procedes d'analyse par diffraction des rayons X qui permettent de produire des motifs de diffraction des rayons X a resolution assez elevee pour la determination de la structure tridimensionnelle de la proteine, ainsi que des procedes d'elaboration rationnelle de substances therapeutiques, bases sur l'utilisation de donnees de sequences d'acides amines et/ou de donnees de cristallographie aux rayons X fournies sur des supports lisibles par ordinateur puis analysees sur un systeme informatique dote d'algorithmes de calcul appropries.

=> d l4 ti 1-43

L4 ANSWER 1 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Inherited metabolic diseases caused by the genetic defect of protective protein/cathepsin A and lysosomal sialidase

L4 ANSWER 2 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Structural and functional study of K453E mutant **protective protein/cathepsin A** causing the late infantile form of **galactosialidosis**

L4 ANSWER 3 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Fetal diagnosis of **galactosialidosis** (**protective protein/cathepsin A** deficiency)

L4 ANSWER 4 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Processing of lysosomal .beta.-galactosidase. The C-terminal precursor fragment is an essential domain of the mature enzyme

L4 ANSWER 5 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Protein **PPCA** (protective protein/catepsin A) and endothelin 1 in **galactosialidosis**

L4 ANSWER 6 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Endothelin-1 in the brain of patients with galactosialidosis: its abnormal increase and distribution pattern

L4 ANSWER 7 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Molecular basis of GM1 gangliosidosis and Morquio disease, type B. Structure-function studies of lysosomal .beta.-galactosidase and the non-lysosomal .beta.-galactosidase-like protein

L4 ANSWER 8 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Stable expression of **protective protein/cathepsin A**-green fluorescent protein fusion genes in a fibroblastic cell line from a **galactosialidosis** patient: model system for revealing the intracellular transport of normal and mutated lysosomal enzymes

L4 ANSWER 9 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Correction of murine **galactosialidosis** by bone marrow-derived macrophages overexpressing human **protective protein/cathepsin a** under control of the colony-stimulating factor-1 receptor promoter

L4 ANSWER 10 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Lack of **PPCA** expression only partially coincides with lysosomal storage in **galactosialidosis** mice: indirect evidence for spatial requirement of the catalytic rather than the protective function of **PPCA**

L4 ANSWER 11 OF 43 CAPLUS COPYRIGHT 2003 ACS
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TI The atomic model of the human **protective protein/cathepsin A** suggests a structural basis for **galactosialidosis**

L4 ANSWER 14 OF 43 CAPLUS COPYRIGHT 2003 ACS
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L4 ANSWER 17 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Molecular and biochemical analysis of **protective protein /cathepsin A** mutations: correlation with clinical severity in **galactosialidosis**

L4 ANSWER 18 OF 43 CAPLUS COPYRIGHT 2003 ACS
TI Mouse model for the lysosomal disorder galactosialidosis and correction of the phenotype with overexpressing erythroid precursor cells

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TIEN PROTEIN SPECIFIC FOR CARDIAC AND SKELETAL MUSCLE
TIFR PROTEINE SPECIFIQUE DES MUSCLES CARDIAQUE ET SQUELETTIQUE

L4 ANSWER 42 OF 43 PCTFULL COPYRIGHT 2003 Univentio
TIEN SECRETED PROTEINS AND USES THEREOF
TIFR PROTEINES SECRETEES ET LEURS UTILISATIONS

L4 ANSWER 43 OF 43 PCTFULL COPYRIGHT 2003 Univentio

TIEN **PROTECTIVE PROTEIN/CATHEPSIN A** AND PRECURSOR: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION AND RATIONAL DRUG DESIGN

TIFR PROTEINE/CATHEPSINE A PROTECTRICE ET PRECURSEUR: CRISTALLISATION, DIFFRACTION DES RAYONS X, DETERMINATION DE STRUCTURE TRIDIMENSIONNELLE ET ELABORATION RATIONNELLE DE SUBSTANCES THERAPEUTIQUES

=> d 1-2

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 190087-33-3 REGISTRY
CN **Glycoprotein PPCA (human protective protein/cathepsin A) (9CI)**
    (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
              1 REFERENCES IN FILE CA (1962 TO DATE)
              1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L5 ANSWER 33 OF 54 DGENE (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: AAB01418 Protein DGENE
TITLE: Novel nucleic acid molecule encoding secreted or membrane-associated proteins useful for identifying modulators and for treating disorders associated with spleen, bone, kidney, liver, pituitary and thyroid gland
INVENTOR: Sharp J D
PATENT ASSIGNEE: (MILL-N)MILLENNIUM PHARM INC.
PATENT INFO: **WO 2000039150 A2 20000706** **129p**
APPLICATION INFO: WO 1999-US31158 19991229
PRIORITY INFO: US 1998-223094 19981230
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-465732 [40]

AB Human TANGO 221 and 222 nucleic acids, proteins and their modulators are useful for modulating adipocyte function and adipocyte disorders such as obesity and for treating disorders associated with abnormal fat metabolism e.g. cachexia and proliferation disorders such as cancer. Further TANGO 222 nucleic acids and proteins are useful for treating disorders associated with spleen and hepatic disorders such as jaundice, hepatitis, cirrhosis or malignant tumors. TANGO 176 nucleic acids, polypeptides and their modulators are useful for treating lysosomal **protective protein cathepsin A** -associated disorders such as **galactosialidosis** and disorders associated with a defect in neutrophil or monocyte chemotaxis. They are also useful for treating renal disorders, intestinal disorders, pituitary related disorders, adrenal cortex disorders such as hypoadrenalism, hyperadrenalism or neoplasia and disorders of the thyroid gland. TANGO 232 nucleic acids, proteins and their modulators are useful for treating cartilage and bone associated disease and disorders such as bone cancer and osteoarthritis.

See entire publ, especially

use of TANGO 176 Polypeptide → P27 L 21 to P28 L 6

Proteins – P50 L 32 to P65

Recomb Exp P65 – 72

Pharmaceutical compns 72 – 76

=> d ibib ab 8

L4 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:399604 HCAPLUS
DOCUMENT NUMBER: 131:168793
TITLE: Stable expression of **protective protein/cathepsin A**-green fluorescent protein fusion genes in a fibroblastic cell line from a **galactosialidosis** patient: model system for revealing the intracellular transport of normal and mutated lysosomal enzymes
AUTHOR(S): Naganawa, Yasunori; Itoh, Kohji; Shimmoto, Michie; Kamei, Sachiko; Takiguchi, Kyoko; Doi, Hirofumi; Sakuraba, Hitoshi
CORPORATE SOURCE: Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo, 113-8613, Japan
SOURCE: Biochemical Journal (**1999**), 340(2), 467-474
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fibroblastic cell lines derived from a **galactosialidosis** patient, stably expressing the chimeric green fluorescent protein variant (EGFP) gene fused to the wild-type and mutant human lysosomal **protective protein/cathepsin A** (**PPCA**) cDNA, were first established as a model system for revealing the sorting and processing of lysosomal enzymes and for investigating the mol. bases of their deficiencies. In the cell line expressing the wild-type **PPCA**-EGFP chimera gene (EGFP-PPwild), an 81 kDa form (27 kDa EGFP fused to the C-terminus of the 54 kDa **PPCA** precursor) was produced, then processed into the mature 32/20 kDa two-chain form free of the EGFP domain. The intracellular cathepsin A, .alpha.-N-acetylneuraminidase and .beta.-galactosidase activities, which are deficient in the parent fibroblastic cells, could also be significantly restored in the cells. In contrast with the uniform and strong fluorescence throughout the cytoplasm and nucleus in the mock-cell line expressing only EGFP cDNA, weak reticular and punctate fluorescence was distributed throughout the EGFP-PPwild cell line. Bafilomycin A1, a potent inhibitor of vacuolar ATPase and intracellular acidification, induced the distribution of Golgi-like perinuclear fluorescence throughout the living and fixed cells, in which only the 81 kDa product was detected. After removal of the agent, time-dependent transport of the chimeric protein from the Golgi app. to the prelysosomal structure in living cells was monitored with a confocal laser scanning microscope system. Leupeptin caused the distribution of lysosome-like granular fluorescence throughout the cytoplasm in the fixed cells, although it was hardly obsd. in living cells. The latter agent also dose-dependently induced an increase in the intracellular amt. of the 81 kDa product contg. the EGFP domain and inhibited the restoration of cathepsin A activity in the EGFP-PPwild cells after the removal of bafilomycin A1. In parallel, both the mature two-chain form and **PPCA** function disappeared. These results suggested that the chimera gene product was transported to acidic compartments (endosomes/lysosomes), where proteolytic processing of the **PPCA** precursor/zymogen, quenching of the fluorescence, and random degrdn. of the EGFP portion occurred. A cell line stably expressing a chimeric gene with a mutant **PPCA** cDNA contg. an A1184 .fwdarw. G (Y395C) mutation, commonly detected in Japanese severe early-infantile type of **galactosialidosis** patients, showed an endoplasmic reticulum (ER)-like reticular fluorescence pattern. The **PPCA** -immunoreactive gene product was hardly detected in this cell line. The mutant chimeric product was suggested to be degraded rapidly in the ER before transport to post-ER compartments. A cell line expressing the chimeric gene with a T746 .fwdarw. A (Y249N) **PPCA** mutation exhibited both ER-like reticular and granular fluorescence on the reticular structure that was stronger than that in the EGFP-PPwild cells. Some of them contained large fluorescent inclusion-body-like structures. The ineffectiveness of transport inhibitors in the distribution changes in the two mutant chimeric proteins suggested that they were not delivered to

acidic compartments. Therefore this expression system can possibly be applied to the direct anal. of the sorting defects of mutant gene products in living cells and will be useful for the mol. investigation of lysosomal diseases, including **galactosialidosis**.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ab 9

L4 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:805590 HCAPLUS
DOCUMENT NUMBER: 130:163159
TITLE: Correction of murine **galactosialidosis** by bone marrow-derived macrophages overexpressing human **protective protein/cathepsin a** under control of the colony-stimulating factor-1 receptor promoter
AUTHOR(S): Hahn, Christopher N.; Del Pilar Martin, Maria; Zhou, Xiao-Yan; Mann, Linda W.; D'Azzo, Alessandra
CORPORATE SOURCE: Department of Genetics, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(25), 14880-14885
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Galactosialidosis** (GS) is a human neurodegenerative disease caused by a deficiency of lysosomal **protective protein /cathepsin A** (**PPCA**). The GS mouse model resembles the severe human condition, resulting in nephropathy, ataxia, and premature death. To rescue the disease phenotype, GS mice were transplanted with bone marrow from transgenic mice overexpressing human **PPCA** specifically in monocytes/macrophages under the control of the colony stimulating factor-1 receptor promoter. Transgenic macrophages infiltrated and resided in all organs and expressed **PPCA** at high levels. Correction occurred in hematopoietic tissues and nonhematopoietic organs, including the central nervous system. **PPCA**-expressing perivascular and leptomeningeal macrophages were detected throughout the brain of recipient mice, although some neuronal cells, such as Purkinje cells, continued to show storage and died. GS mice crossed into the transgenic background reflected the outcome of bone marrow-transplanted mice, but the course of neuronal degeneration was delayed in this model. These studies present definite evidence that macrophages alone can provide a source of corrective enzyme for visceral organs and may be beneficial for neuronal correction if expression levels are sufficient.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ab 19

L4 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:927266 HCAPLUS
DOCUMENT NUMBER: 123:336634
TITLE: Mouse model for the lysosomal disorder galactosialidosis and correction of the phenotype with overexpressing erythroid precursor cells
AUTHOR(S): Zhou, Xiao Yan; Morreau, Hans; Rottier, Robbert; Davis, Donna; Bonten, Erik; Gillemans, Nynke; Wenger, David; Grosveld, Frank G.; Doherty, Peter; et al.
CORPORATE SOURCE: Department Genetics, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Genes & Development (**1995**), 9(21), 2623-34
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The lysosomal storage disorder **galactosialidosis** results from a primary deficiency of the **protective protein/ cathepsin A** (**PPCA**), which in turn affects the activities of .beta.-galactosidase and neuraminidase. Mice homozygous for a null mutation at the **PPCA** locus present with signs of the disease shortly after birth and develop a phenotype closely resembling human patients with **galactosialidosis**. Most of their tissues show characteristic vacuolation of specific cells, attributable to lysosomal storage. Excessive excretion of sialyloligosaccharides in urine is diagnostic of the disease. Affected mice progressively deteriorate as a consequence of severe organ dysfunction, esp. of the kidney. The deficient phenotype can be cor. by transplanting null mutants with bone marrow from a transgenic line overexpressing human **PPCA** in erythroid precursor cells. The transgenic bone marrow gives a more efficient and complete correction of the visceral organs than normal bone marrow. The data demonstrate the usefulness of this animal model, very similar to the human disease, for experimenting therapeutic strategies aimed to deliver the functional protein or gene to affected organs. Furthermore, they suggest the feasibility of gene therapy for **galactosialidosis** and other disorders, using bone marrow cells engineered to overexpress and secrete the correcting lysosomal protein.

L5 ANSWER 13 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:210129 BIOSIS
DOCUMENT NUMBER: PREV199800210129
TITLE: Transport of human lysosomal neuraminidase to mature lysosomes requires protective protein/cathepsin A.
AUTHOR(S): van Der Spoel, Aarnoud; Bonten, Erik; D'Azzo, Alessandra (1)
CORPORATE SOURCE: (1) Dep. Genet., St. Jude Child. Res. Hosp., 332 North Lauderdale, Memphis, TN 38105 USA
SOURCE: EMBO (European Molecular Biology Organization) Journal, (**March 16, 1998**) Vol. 17, No. 6, pp. 1588-1597.
ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Human lysosomal N-acetyl-alpha-neuraminidase is deficient in two lysosomal storage disorders, sialidosis, caused by structural mutations in the neuraminidase gene, and **galactosialidosis**, in which a primary defect of **protective protein/cathepsin A** (**PPCA**) leads to a combined deficiency of neuraminidase and beta-D-galactosidase. These three glycoproteins can be isolated in a high molecular weight multi-enzyme complex, and the enzymatic activity of neuraminidase is contingent on its interaction with **PPCA**. To explain the unusual need of neuraminidase for an auxiliary protein, we examined, in transfected COS-1 cells, the effect of **PPCA** expression on post-translational modification, turnover and intracellular localization of neuraminidase. In pulse-chase studies, we show that the enzyme is synthesized as a 46 kDa glycoprotein, which is poorly phosphorylated, does not undergo major proteolytic processing and is secreted. Importantly, its half-life is not altered by the presence of **PPCA**. However, neuraminidase associates with the **PPCA** precursor shortly after synthesis, since the latter protein coprecipitates with neuraminidase using anti-neuraminidase antibodies. We further demonstrate by subcellular fractionation of transfected cells that neuraminidase segregates to mature lysosomes only when accompanied by wild-type **PPCA**, but not by transport-impaired **PPCA** mutants. These data suggest a novel role for **PPCA** in the activation of lysosomal neuraminidase, that of an intracellular transport protein.

L5 ANSWER 14 OF 54 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1999:1788 SCISEARCH
THE GENUINE ARTICLE: 141AW
TITLE: Bicistronic retroviral vector coexpressing lysosomal **protective protein cathepsin A** and GFP for gene therapy of **galactosialidosis**
AUTHOR: Leimig T (Reprint); Persons D; Allay J A; Nienhuis A W; dAzzo A
CORPORATE SOURCE: ST JUDE CHILDRENS HOSP, MEMPHIS, TN 38105
COUNTRY OF AUTHOR: USA
SOURCE: BLOOD, (**15 NOV 1998**) Vol. 92, No. 10, Part 1, Supp. [1], pp. 1223-1223.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

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=> d his

     (FILE 'HOME' ENTERED AT 11:11:10 ON 13 MAR 2003)

     FILE 'HCAPLUS' ENTERED AT 11:11:27 ON 13 MAR 2003
L1           111 S GALACTOSIALIDOSIS OR (SIALIC ACIDS (L) GALACTOSIALIDOSIS)
L2            21 S L1 (L) (PROTECTIVE PROTEIN CATHEPSIN A OR PPCA)
L3            19 S L2 AND PD<20010928
L4            19 S L2 AND PD<20000928
```

=> d ibib ab 1-19

L4 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:749414 HCAPLUS
DOCUMENT NUMBER: 133:279607
TITLE: Inherited metabolic diseases caused by the genetic defect of protective protein/cathepsin A and lysosomal sialidase
AUTHOR(S): Itoh, Kohji
CORPORATE SOURCE: Inst. Med. Resour., Fac. Pharm. Sci., The Univ. Tokushima, 1-78 Sho-Machi, Tokushima, 770-8505, Japan
SOURCE: Seikagaku (**2000**), 72(9), 1160-1164
CODEN: SEIKAQ; ISSN: 0037-1017
PUBLISHER: Nippon Seikagakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 15 refs., on the mol. pathogenesis of **galactosialidosis** (GS) and sialidosis (SD). The role of **protective protein/cathepsin A** (**PPCA**) in the pathogenesis of GS, a defect in the degrdn. of endothelin-1 due to the mutations in **PPCA** in GS patients, three-dimensional structure of **PPCA** precursor, cDNA cloning and amino acid sequence of human lysosomal sialidase (Sial), importance of **PPCA** in the expression of Sial activity in lysosome, and mutations in the gene for Sial in the patients with SD are discussed.

L4 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:575050 HCAPLUS
DOCUMENT NUMBER: 134:129731
TITLE: Structural and functional study of K453E mutant **protective protein/cathepsin A** causing the late infantile form of **galactosialidosis**
AUTHOR(S): Takiguchi, Kyoko; Itoh, Kohji; Shimmoto, Michie; Ozand, Pinar T.; Doi, Hirofumi; Sakuraba, Hitoshi
CORPORATE SOURCE: Fujitsu Laboratories Ltd., Chiba, Japan
SOURCE: Journal of Human Genetics (**2000**), 45(4), 200-206
CODEN: JHGEFR; ISSN: 1434-5161
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To clarify the mol. basis of the late infantile form of **galactosialidosis**, the authors characterized a defective **protective protein/cathepsin A** (**PPCA**) gene product with the K453E mutation newly found in an Arabic patient with this disease. Immunocytochem., expression, and metabolic studies revealed that the precursor **PPCA** was synthesized but not processed to the mature form, and it was degraded in the mutant. A structural model of the mutant **PPCA** was constructed by amino acid substitution of 453glutamic acid for lysine in the crystal structure of the wild type **PPCA** precursor reported. The results show that the K453E mutation is located at the dimer interface of the **PPCA** and reduces the hydrogen bond formation in the dimer. This structural change may cause instability of the **PPCA** dimer.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:404042 HCAPLUS
Correction of: 1997:747939
DOCUMENT NUMBER: 133:3383
Correction of: 128:113691
TITLE: Fetal diagnosis of **galactosialidosis** (**protective protein/cathepsin A** deficiency)
AUTHOR(S): Itoh, Kohji; Miharu, Norio; Ohama, Koso; Mizoguchi, Nobuyuki; Sakura, Nobuo; Sakuraba, Hitoshi

CORPORATE SOURCE: The Tokyo Metropolitan Institute of Medical Science, Tokyo, 113, Japan
SOURCE: Clinica Chimica Acta (**1997**), 266(2), 75-82
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The fetal diagnosis of **galactosialidosis** is performed by measuring carboxypeptidase (cathepsin A) activity in cultured villus cells and by immunofluorescence anal. with an antibody against an oligopeptide corresponding to the N-terminal domain of the human mature protective protein. Neither carboxypeptidase activity nor immunofluorescence was detected in cultured villus cells derived from an at-risk fetus or in cultured fibroblasts derived from the sister with **galactosialidosis**. Neuraminidase and .beta.-galactosidase activities were also confirmed to be deficient or low. A direct assay system for **protective protein/cathepsin A** is useful for the accurate prenatal diagnosis of **galactosialidosis**.

L4 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:251005 HCAPLUS
DOCUMENT NUMBER: 133:39862
TITLE: Processing of lysosomal .beta.-galactosidase. The C-terminal precursor fragment is an essential domain of the mature enzyme
AUTHOR(S): Van der Spoel, Aarnoud; Bonten, Erik; D'Azzo, Alessandra
CORPORATE SOURCE: Department of Genetics, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Journal of Biological Chemistry (**2000**), 275(14), 10035-10040
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lysosomal .beta.-D-galactosidase (.beta.-gal), the enzyme deficient in the autosomal recessive disorders GM1 gangliosidosis and Morquio B, is synthesized as an 85-kDa precursor that is C-terminally processed into a 64-66-kDa mature form. The released .apprx.20-kDa proteolytic fragment was thought to be degraded. We now present evidence that it remains assocd. to the 64-kDa chain after partial proteolysis of the precursor. This polypeptide was found to copurify with .beta.-gal and **protective protein/cathepsin A** from mouse liver and Madin-Darby bovine kidney cells and was immunopptd. from human fibroblasts but not from fibroblasts of a GM1 gangliosidosis and a **galactosialidosis** patient. Uptake of wild-type **protective protein/cathepsin A** by **galactosialidosis** fibroblasts resulted in a significant increase of mature and active .beta.-gal and its C-terminal fragment. Expression in COS-1 cells of mutant cDNAs encoding either the N-terminal or the C-terminal domain of .beta.-gal resulted in the synthesis of correctly sized polypeptides without catalytic activity. When co-expressed, the two subunits assoc. and become catalytically active. Our results suggest that the C terminus of .beta.-gal is an essential domain of the catalytically active enzyme and provide evidence that lysosomal .beta.-galactosidase is a two-subunit mol. These data may give new significance to mutations in GM1 gangliosidosis patients found in the C-terminal part of the mol.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:140724 HCAPLUS
DOCUMENT NUMBER: 133:57128
TITLE: Protein **PPCA** (protective protein/catepsin A) and endothelin 1 in **galactosialidosis**
AUTHOR(S): Ito, Koji
CORPORATE SOURCE: Div. Clin. Genet., The Tokyo Metrop. Inst. Med. Sci.,

Japan
SOURCE: Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku (**2000**), Volume Date 1998, 17, 117-121
CODEN: IOKHEP; ISSN: 0914-5117
PUBLISHER: Ikagaku Oyo Kenkyu Zaidan
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Protective protein/catepsin A like protein (**PPCA**), whose deficiency causes **galactosialidosis** (GS), possessed endothelin 1 (ET-1) degrdn. activity, and ET-1 tissue content increased in GS. **PPCA** was detected some tissues as Golgi cells of granule layer, Purkinje's cells in cerebellum in healthy control whereas no **PPCA** was detected in GS patients' cerebellum. ET-1 signal was much stronger in GS than healthy control except Purkinje's cells. ET-1 signal also enhanced in cerebellar cortex, hippocampus and anterior horn of spinal cord. Addn. of antisense oligonucleotide for **PPCA** to mouse cells derived from cerebellum of embryo and neonatal baby increased ET-1 content. The mutant **PPCA** of GS patients showed different localization compared with wild **PPCA**.

L4 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:60988 HCAPLUS
DOCUMENT NUMBER: 132:320573
TITLE: Endothelin-1 in the brain of patients with galactosialidosis: its abnormal increase and distribution pattern
AUTHOR(S): Itoh, Kohji; Oyanagi, Kiyomitsu; Takahashi, Hitoshi; Sato, Takeshi; Hashizume, Yoshio; Shimmoto, Michie; Sakuraba, Hitoshi
CORPORATE SOURCE: Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
SOURCE: Annals of Neurology (**2000**), 47(1), 122-126
CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelin-1 is a peptidic substrate in vitro of lysosomal **protective protein/cathepsin A** (**PPCA**) with serine carboxypeptidase activity. Endothelin-1-specific immunoreactivity has been demonstrated to be markedly increased and distributed abnormally in the neurons and glial cells within autopsied brain regions, including the cerebellum, hippocampal formation, and spinal cord, of patients affected with **galactosialidosis**, a human **PPCA** deficiency. The genetic defect of the endothelin-1 degrading activity of **PPCA** is suggested to cause some of the neurol. abnormalities of this disease.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:737285 HCAPLUS
DOCUMENT NUMBER: 132:21594
TITLE: Molecular basis of GM1 gangliosidosis and Morquio disease, type B. Structure-function studies of lysosomal .beta.-galactosidase and the non-lysosomal .beta.-galactosidase-like protein
AUTHOR(S): Callahan, John W.
CORPORATE SOURCE: Structural Biology and Biochemistry, The Research Institute and Genetic-Metabolic Laboratory, Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, and the Department of Biochemistry, University of Toronto, Toronto, ON, M5G 1X8, Can.
SOURCE: Biochimica et Biophysica Acta (**1999**), 1455(2-3), 85-103
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 113 refs. GM1 gangliosidosis and Morquio B disease are distinct disorders both clin. and biochem. yet they arise from the same .beta.-galactosidase enzyme deficiency. On the other hand, **galactosialidosis** and sialidosis share common clin. and biochem. features, yet they arise from two sep. enzyme deficiencies, namely, **protective protein/cathepsin A** and neuraminidase, resp. However distinct, in practice these disorders overlap both clin. and biochem. so that easy discrimination between them is sometimes difficult. The principle reason for this may be found in the fact that these three enzymes form a unique complex in lysosomes that is required for their stability and posttranslational processing. In this review, I focus mainly on the primary and secondary .beta.-galactosidase deficiency states and offer some hypotheses to account for differences between GM1 gangliosidosis and Morquio B disease.

REFERENCE COUNT: 113 THERE ARE 113 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:399604 HCAPLUS

DOCUMENT NUMBER: 131:168793

TITLE: Stable expression of **protective protein/cathepsin A**-green fluorescent protein fusion genes in a fibroblastic cell line from a **galactosialidosis** patient: model system for revealing the intracellular transport of normal and mutated lysosomal enzymes

AUTHOR(S): Naganawa, Yasunori; Itoh, Kohji; Shimmoto, Michie; Kamei, Sachiko; Takiguchi, Kyoko; Doi, Hirofumi; Sakuraba, Hitoshi

CORPORATE SOURCE: Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo, 113-8613, Japan

SOURCE: Biochemical Journal (**1999**), 340(2), 467-474
CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fibroblastic cell lines derived from a **galactosialidosis** patient, stably expressing the chimeric green fluorescent protein variant (EGFP) gene fused to the wild-type and mutant human lysosomal **protective protein/cathepsin A** (**PPCA**) cDNA, were first established as a model system for revealing the sorting and processing of lysosomal enzymes and for investigating the mol. bases of their deficiencies. In the cell line expressing the wild-type **PPCA**-EGFP chimera gene (EGFP-PPwild), an 81 kDa form (27 kDa EGFP fused to the C-terminus of the 54 kDa **PPCA** precursor) was produced, then processed into the mature 32/20 kDa two-chain form free of the EGFP domain. The intracellular cathepsin A, .alpha.-N-acetylneuraminidase and .beta.-galactosidase activities, which are deficient in the parent fibroblastic cells, could also be significantly restored in the cells. In contrast with the uniform and strong fluorescence throughout the cytoplasm and nucleus in the mock-cell line expressing only EGFP cDNA, weak reticular and punctate fluorescence was distributed throughout the EGFP-PPwild cell line. Bafilomycin A1, a potent inhibitor of vacuolar ATPase and intracellular acidification, induced the distribution of Golgi-like perinuclear fluorescence throughout the living and fixed cells, in which only the 81 kDa product was detected. After removal of the agent, time-dependent transport of the chimeric protein from the Golgi app. to the prelysosomal structure in living cells was monitored with a confocal laser scanning microscope system. Leupeptin caused the distribution of lysosome-like granular fluorescence throughout the cytoplasm in the fixed cells, although it was hardly obsd. in living cells. The latter agent also dose-dependently induced an increase in the intracellular amt. of the 81 kDa product contg. the EGFP domain and inhibited the restoration of cathepsin A activity in the EGFP-PPwild cells after the removal of bafilomycin A1. In parallel, both the mature two-chain form and **PPCA** function disappeared. These results suggested that the chimera gene product was transported to acidic

compartments (endosomes/lysosomes), where proteolytic processing of the **PPCA** precursor/zymogen, quenching of the fluorescence, and random degrdn. of the EGFP portion occurred. A cell line stably expressing a chimeric gene with a mutant **PPCA** cDNA contg. an A1184 .fwdarw. G (Y395C) mutation, commonly detected in Japanese severe early-infantile type of **galactosialidosis** patients, showed an endoplasmic reticulum (ER)-like reticular fluorescence pattern. The **PPCA** -immunoreactive gene product was hardly detected in this cell line. The mutant chimeric product was suggested to be degraded rapidly in the ER before transport to post-ER compartments. A cell line expressing the chimeric gene with a T746 .fwdarw. A (Y249N) **PPCA** mutation exhibited both ER-like reticular and granular fluorescence on the reticular structure that was stronger than that in the EGFP-PPwild cells. Some of them contained large fluorescent inclusion-body-like structures. The ineffectiveness of transport inhibitors in the distribution changes in the two mutant chimeric proteins suggested that they were not delivered to acidic compartments. Therefore this expression system can possibly be applied to the direct anal. of the sorting defects of mutant gene products in living cells and will be useful for the mol. investigation of lysosomal diseases, including **galactosialidosis**.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:805590 HCAPLUS

DOCUMENT NUMBER: 130:163159

TITLE: Correction of murine **galactosialidosis** by bone marrow-derived macrophages overexpressing human **protective protein/cathepsin a** under control of the colony-stimulating factor-1 receptor promoter

AUTHOR(S): Hahn, Christopher N.; Del Pilar Martin, Maria; Zhou, Xiao-Yan; Mann, Linda W.; D'Azzo, Alessandra

CORPORATE SOURCE: Department of Genetics, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(25), 14880-14885
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Galactosialidosis** (GS) is a human neurodegenerative disease caused by a deficiency of lysosomal **protective protein /cathepsin A** (**PPCA**). The GS mouse model resembles the severe human condition, resulting in nephropathy, ataxia, and premature death. To rescue the disease phenotype, GS mice were transplanted with bone marrow from transgenic mice overexpressing human **PPCA** specifically in monocytes/macrophages under the control of the colony stimulating factor-1 receptor promoter. Transgenic macrophages infiltrated and resided in all organs and expressed **PPCA** at high levels. Correction occurred in hematopoietic tissues and nonhematopoietic organs, including the central nervous system. **PPCA**-expressing perivascular and leptomeningeal macrophages were detected throughout the brain of recipient mice, although some neuronal cells, such as Purkinje cells, continued to show storage and died. GS mice crossed into the transgenic background reflected the outcome of bone marrow-transplanted mice, but the course of neuronal degeneration was delayed in this model. These studies present definite evidence that macrophages alone can provide a source of corrective enzyme for visceral organs and may be beneficial for neuronal correction if expression levels are sufficient.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:647597 HCAPLUS

DOCUMENT NUMBER: 130:21269

TITLE: Lack of **PPCA** expression only partially coincides with lysosomal storage in

galactosialidosis mice: indirect evidence for spatial requirement of the catalytic rather than the protective function of **PPCA**

AUTHOR(S): Rottier, Robbert J.; Hahn, Christopher N.; Mann, Linda W.; Martin, Maria del Pilar; Smeyne, Richard J.; Suzuki, Kinuko; D'Azzo, Alessandra

CORPORATE SOURCE: Dep. Genetics, St. Jude Children's Res. Hosp., Memphis, TN, 38105, USA

SOURCE: Human Molecular Genetics (**1998**), 7(11), 1787-1794
CODEN: HMGEE5; ISSN: 0964-6906

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Protective protein/cathepsin A** (**PPCA**) is a pleiotropic lysosomal enzyme that complexes with .beta.-galactosidase and neuraminidase, and possesses serine carboxypeptidase activity. Its deficiency in man results in the neurodegenerative lysosomal storage disorder **galactosialidosis** (GS). The mouse model of this disease resembles the human early onset phenotype and results in severe nephropathy and ataxia. To understand better the pathophysiol. of the disease, the authors compared the occurrence of lysosomal **PPCA** mRNA and protein in normal adult mouse tissues with the incidence of lysosomal storage in **PPCA** (-/-) mice. **PPCA** expression was markedly variable among different tissues. Most sites that produced both mRNA and protein at high levels in normal mice showed extensive and overt storage in the knockout mice. However, this correlation was not consistent as some cells that normally expressed high levels of **PPCA** were unaffected in their storage capability in the **PPCA**(-/-) mice. In addn., some normally low expressing cells accumulated large amts. of undegraded products in the GS mouse. This apparent discrepancy may reflect a requirement for the catalytic rather than the protective function of **PPCA** and/or the presence of cell-specific substrates in certain cell types. A detailed map showing the cellular distribution of **PPCA** in normal mouse tissues as well as the sites of lysosomal storage in deficient mice is crit. for accurate assessment of the effects of therapeutic interventions.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:379960 HCAPLUS

DOCUMENT NUMBER: 129:121146

TITLE: **Protective protein/cathepsin A** loss in cultured cells derived from an early-infantile form of **galactosialidosis** patients homozygous for the A1184-G transition (Y395C mutation)

AUTHOR(S): Itoh, Kohji; Shimmoto, Michie; Utsumi, Kouichi; Mizoguchi, Nobuyuki; Miharu, Norio; Ohama, Koso; Sakuraba, Hitoshi

CORPORATE SOURCE: Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo, 113-8613, Japan

SOURCE: Biochemical and Biophysical Research Communications (**1998**), 247(1), 12-17
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Galactosialidosis** is a human autosomal recessive lysosomal storage disease caused by a genetic defect of **protective protein/cathepsin A** (**PPCA**). The patients in a Japanese family with the severe early-infantile form of **galactosialidosis** were revealed to be homozygous for the A1184-G transition in the **PPCA** gene in both alleles, which leads to the Y395C substitution. The acid carboxypeptidase (cathepsin A) and lysosomal neuraminidase activities were markedly decreased in cultured fibroblasts

and chorionic villus cells derived from the patients, although the decrease in .beta.-galactosidase activity was less. Immunoblot and immunocytochem. analyses showed that neither the precursor nor the mature form of the **PPCA** gene product was present in the cultured cells. The Y395C mutation was revealed to cause the loss of the translated product, that dets. the severity of the clin. phenotype. (c) 1998 Academic Press.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:225141 HCAPLUS

DOCUMENT NUMBER: 129:14642

TITLE: Transport of human lysosomal neuraminidase to mature lysosomes requires protective protein/cathepsin A

AUTHOR(S): Van Der Spoel, Aarnoud; Bonten, Erik; D'azzo, Alessandra

CORPORATE SOURCE: Department of Genetics, St Jude Children's Research Hospital, Memphis, TN, 38105, USA

SOURCE: EMBO Journal (**1998**), 17(6), 1588-1597
CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human lysosomal N-acetyl-.alpha.-neuraminidase is deficient in two lysosomal storage disorders, sialidosis, caused by structural mutations in the neuraminidase gene, and **galactosialidosis**, in which a primary defect of **protective protein/cathepsin A** (**PPCA**) leads to a combined deficiency of neuraminidase and .beta.-D-galactosidase. These three glycoproteins can be isolated in a high mol. wt. multi-enzyme complex, and the enzymic activity of neuraminidase is contingent on its interaction with **PPCA**. To explain the unusual need of neuraminidase for an auxiliary protein, we examd., in transfected COS-1 cells, the effect of **PPCA** expression on post-translational modification, turnover and intracellular localization of neuraminidase. In pulse-chase studies, we show that the enzyme is synthesized as a 46 kDa glycoprotein, which is poorly phosphorylated, does not undergo major proteolytic processing and is secreted. Importantly, its half-life is not altered by the presence of **PPCA**. However, neuraminidase assocs. with the **PPCA** precursor shortly after synthesis, since the latter protein coppts. with neuraminidase using anti-neuraminidase antibodies. We further demonstrate by subcellular fractionation of transfected cells that neuraminidase segregates to mature lysosomes only when accompanied by wild-type **PPCA**, but not by transport-impaired **PPCA** mutants. These data suggest a novel role for **PPCA** in the activation of lysosomal neuraminidase, that of an intracellular transport protein.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:61203 HCAPLUS

DOCUMENT NUMBER: 128:165919

TITLE: The atomic model of the human **protective protein/cathepsin A** suggests a structural basis for **galactosialidosis**

AUTHOR(S): Rudenko, Gabby; Bonten, Erik; Hol, Wim. G. J.; D'azzo, Alessandra

CORPORATE SOURCE: Department of Biological Structure, Howard Hughes Medical Institute, University of Washington, Seattle, WA, 98195-7742, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(2), 621-625
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human **protective protein/cathepsin A** (**PPCA**), a serine carboxypeptidase, forms a multienzyme complex with .beta.-galactosidase and neuraminidase and is required for the intralysosomal activity and stability of these two glycosidases. Genetic lesions in **PPCA** lead to a deficiency of .beta.-galactosidase and neuraminidase that is manifest as the autosomal recessive lysosomal storage disorder **galactosialidosis**. Eleven amino acid substitutions identified in mutant **PPCAs** from clin. different **galactosialidosis** patients have now been modeled in the three-dimensional structure of the wild-type enzyme. Of these substitutions, 9 are located in positions likely to alter drastically the folding and stability of the variant protein. In contrast, the other 2 mutations that are assocd. with a more moderate clin. outcome and are characterized by residual mature protein appeared to have a milder effect on protein structure. Remarkably, none of the mutations occurred in the active site or at the protein surface, which would have disrupted the catalytic activity or protective function. Instead, anal. of the 11 mutations revealed a substantive correlation between the effect of the amino acid substitution on the integrity of protein structure and the general severity of the clin. phenotype. The high incidence of **PPCA** folding mutants in **galactosialidosis** reflects the fact that a single point mutation is unlikely to affect both the .beta.-galactosidase and the neuraminidase binding sites of **PPCA** at the same time to produce the double glycosidase deficiency. Mutations in **PPCA** that result in defective folding, however, disrupt every function of **PPCA** simultaneously.

L4 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:747939 HCAPLUS
DOCUMENT NUMBER: 128:113691
TITLE: Fetal diagnosis of **galactosialidosis** (**protective protein/cathepsin A** deficiency)
AUTHOR(S): Itoh, Kohji; Miharu, Norio; Ohama, Koso; Mizoguchi, Nobuyuki; Nobuo Sakura; Sakuraba, Hitoshi
CORPORATE SOURCE: Bunkyo-ku, Honkomagome, Department of Clinical Genetics, The Tokyo Metropolitan Institute of Medical Science, Tokyo, 113, Japan
SOURCE: Clinica Chimica Acta (**1997**), 266(2), 75-82
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The fetal diagnosis of **galactosialidosis** is performed by measuring carboxypeptidase (cathepsin A) activity in cultured villus cells and by immunofluorescence anal. with an antibody against an oligopeptide corresponding to the N-terminal domain of the human mature protective protein. Neither carboxypeptidase activity nor immunofluorescence was detected in cultured villus cells derived from an at-risk fetus or in cultured fibroblasts derived from the sister with **galactosialidosis**. Neuraminidase and .beta.-galactosidase activities were also confirmed to be deficient or low. A direct assay system for **protective protein/cathepsin A** is useful for the accurate prenatal diagnosis of **galactosialidosis**.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:357195 HCAPLUS
DOCUMENT NUMBER: 127:76741
TITLE: Identification of the promoters for the human and murine protective protein/cathepsin A genes
AUTHOR(S): Rottier, Robbert J.; D'Azzo, Alessandra
CORPORATE SOURCE: Dep. Genetics, St. Jude Children's Res. Hospital, Memphis, TN, 38105, USA
SOURCE: DNA and Cell Biology (**1997**), 16(5), 599-610
CODEN: DCEBE8; ISSN: 1044-5498
PUBLISHER: Liebert

DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Protective protein/cathepsin A** (**PPCA**) is a lysosomal serine carboxypeptidase that forms a complex with .beta.-galactosidase and neuraminidase. Its deficiency in humans leads to the lysosomal storage disorder **galactosialidosis** (GS). The pathol. manifestations in patients relate primarily to the severe deficiency of neuraminidase, and the physiol. significance of cathepsin A activity remains unclear. The mouse model of GS, which closely resembles the human phenotype, shows that cells from numerous tissues, esp. the central nervous system (CNS), are affected by this disease. To study the site and level of expression of **PPCA** mRNA in murine and human tissues, the authors analyzed the promoter regions of the corresponding genes. Their 5' genomic regions were strikingly similar in both organization and sequence. A single 1.8-kb **PPCA** transcript is present in humans, whereas mouse tissues have a major 1.8-kb and a minor 2.0-kb transcript, both of which are differentially expressed. These two mouse mRNA species differ only in their 5' untranslated region (UTR). The larger mRNA, unique to mouse, is transcribed from an upstream TATA-box-contg. promoter, which is absent in the human gene. The downstream promoter, which transcribes the 1.8-kb mRNA common to human and mouse, has characteristics of housekeeping gene promoters and contains putative Sp1 binding sites and three USF/MLTF sequences. In vitro studies demonstrated that expression from the downstream promoter is higher than that from the upstream murine-specific promoter. In situ hybridization of mouse tissue sections identified regions of the brain that preferentially express the 2.0-kb transcript. The authors results imply that **PPCA** mRNA distribution and regulation in murine tissues differs from that in human tissues.

L4 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:57474 HCAPLUS
DOCUMENT NUMBER: 126:181965
TITLE: Molecular and biochemical analysis of **protective protein/cathepsin A** mutations: correlation with clinical severity in **galactosialidosis**. [Erratum to document cited in CA126:153428]
AUTHOR(S): Zhou, Xiao-Yan; van der Spoel, Aarnoud; Rottier, Robbert; Hale, Greg; Willemsen, Rob; Berry, Gerard T.; Strisciuglio, Pietro; Morrone, Amelia; Zammarchi, Enrico; Andria, Generoso; d'Azzo, Alessandra
CORPORATE SOURCE: Dep. Genetics, St Jude Children's Res. Hosp., Memphis, TN, 38105, USA
SOURCE: Human Molecular Genetics (**1997**), 6(1), 146
CODEN: HMGEE5; ISSN: 0964-6906
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstr. or the index entries.

L4 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:35104 HCAPLUS
DOCUMENT NUMBER: 126:154393
TITLE: Characterization of human lysosomal neuraminidase defines the molecular basis of the metabolic storage disorder sialidosis
AUTHOR(S): Bonten, Erik; van der Spoel, Aarnoud; Fornerod, Maarten; Grosveld, Gerard; d'Azzo, Alessandra
CORPORATE SOURCE: Dep. Genetics, St. Jude Children's Res. Hosp., Memphis, TN, 38105, USA
SOURCE: Genes & Development (**1996**), 10(24), 3156-3169
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neuraminidases (sialidases) have an essential role in the removal of terminal sialic acid residues from sialoglycoconjugates and are

distributed widely in nature. The human lysosomal enzyme occurs in complex with .beta.-galactosidase and **protective protein /cathepsin A** (**PPCA**), and is deficient in two genetic disorders: sialidosis, caused by a structural defect in the neuraminidase gene, and **galactosialidosis**, in which the loss of neuraminidase activity is secondary to a deficiency of **PPCA**. The authors identified a full-length cDNA clone in the dbEST data base, of which the predicted amino acid sequence has extensive homol. to other mammalian and bacterial neuraminidases, including the F(Y)RIP domain and "Asp-boxes". In situ hybridization localized the human neuraminidase gene to chromosome band 6p21, a region known to contain the HLA locus. Transient expression of the cDNA in deficient human fibroblasts showed that the enzyme is compartmentalized in lysosomes and restored neuraminidase activity in a **PPCA**-dependent manner. The authenticity of the cDNA was verified by the identification of three independent mutations in the open reading frame of the mRNA from clin. distinct sialidosis patients. Coexpression of the mutant cDNAs with **PPCA** failed to generate neuraminidase activity, confirming the inactivating effect of the mutations. These results establish the mol. basis of sialidosis in these patients, and clearly identify the cDNA-encoded protein as lysosomal neuraminidase.

L4 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:757105 HCAPLUS
DOCUMENT NUMBER: 126:153428
TITLE: Molecular and biochemical analysis of **protective protein/cathepsin A** mutations: correlation with clinical severity in **galactosialidosis**
AUTHOR(S): Zhou, Xian-Yan; van der Spoel, Aarnoud; Rottier, Robbert; Hale, Greg; Willemsen, Rob; Berry, Gerard T.; Strisciuglio, Pietro; Andria, Generoso; d'Azzo, Alessandra
CORPORATE SOURCE: Dep. Genet., St Jude Child. Res. Hosp., Memphis, TN, 38105, USA
SOURCE: Human Molecular Genetics (**1996**), 5(12), 1977-1987
CODEN: HMGEE5; ISSN: 0964-6906
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations in the gene encoding lysosomal **protective protein/cathepsin A** (**PPCA**) are the cause of the lysosomal disorder **galactosialidosis** (GS). Depending on age of onset and severity of the symptoms, patients present with either an early infantile (EI), a late infantile (LI), or a juvenile/adult (J/A) form of the disease. To study genotype-phenotype correlation in this disorder, the authors have analyzed the mutations in the **PPCA** gene of eight clin. different patients. In two EI and one J/A patient, the authors have identified four novel point mutations (Val104Met, Leu208Pro, Gly411Ser and Ser23Tyr), that prevent phosphorylation and, hence, lysosomal localization and maturation of the mutant precursors. Two amino acid substitutions (Phe412Val and Tyr221Asn) are shared by five LI patients. These mutations appear to be pathognomonic for this phenotype, and det. the clin. outcome depending on whether they are present together or in combination with other mutations. The latter include a single base deletion and a novel amino acid change (Met378Thr), which generates an addnl. glycosylation site. Within the LI group, patients carrying the Phe412Val mutation are clin. more severe than those with the Tyr221Asn substitution. This is in agreement with the biochem. behavior of the Asn221-mutant protein, i.e., like the Phe412Val protein, phosphorylated, routed to lysosomes and proteolytically processed, but its intralysosomal stability is intermediate between that of wild-type **PPCA** and Val412-**PPCA**. Overall, these results may explain the clin. heterogeneity obsd. in GS patients and may help to correlate mutant allelic combinations with specific clin. phenotypes.

L4 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:927266 HCAPLUS
DOCUMENT NUMBER: 123:336634
TITLE: Mouse model for the lysosomal disorder galactosialidosis and correction of the phenotype with overexpressing erythroid precursor cells
AUTHOR(S): Zhou, Xiao Yan; Morreau, Hans; Rottier, Robbert; Davis, Donna; Bonten, Erik; Gillemans, Nynke; Wenger, David; Grosveld, Frank G.; Doherty, Peter; et al.
CORPORATE SOURCE: Department Genetics, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Genes & Development (**1995**), 9(21), 2623-34
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The lysosomal storage disorder **galactosialidosis** results from a primary deficiency of the **protective protein/cathepsin A** (**PPCA**), which in turn affects the activities of .beta.-galactosidase and neuraminidase. Mice homozygous for a null mutation at the **PPCA** locus present with signs of the disease shortly after birth and develop a phenotype closely resembling human patients with **galactosialidosis**. Most of their tissues show characteristic vacuolation of specific cells, attributable to lysosomal storage. Excessive excretion of sialyloligosaccharides in urine is diagnostic of the disease. Affected mice progressively deteriorate as a consequence of severe organ dysfunction, esp. of the kidney. The deficient phenotype can be cor. by transplanting null mutants with bone marrow from a transgenic line overexpressing human **PPCA** in erythroid precursor cells. The transgenic bone marrow gives a more efficient and complete correction of the visceral organs than normal bone marrow. The data demonstrate the usefulness of this animal model, very similar to the human disease, for experimenting therapeutic strategies aimed to deliver the functional protein or gene to affected organs. Furthermore, they suggest the feasibility of gene therapy for **galactosialidosis** and other disorders, using bone marrow cells engineered to overexpress and secrete the correcting lysosomal protein.

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=> d his

     (FILE 'HOME' ENTERED AT 11:30:57 ON 13 MAR 2003)

     FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
     CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DGENE, DRUGB,
     DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, DRUGUPDATES, ...' ENTERED AT
     11:32:14 ON 13 MAR 2003
L1          1160 S GALACTOSIALIDOSIS OR (SIALIC ACIDS (L) GALACTOSIALIDOSIS)
L2           218 S L1 (L) (PROTECTIVE PROTEIN CATHEPSIN A OR PPCA)
L3            64 DUP REM L2 (154 DUPLICATES REMOVED)
L4            54 S L3 AND PY<2001
L5            54 DUP REM L4 (0 DUPLICATES REMOVED)
L6             0 S L5 AND PHARMA?
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